

ATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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JUN 28 2005

To:

RANBAXY LABORATORIES LIMITED
Attn. Deshmukh, Jay R.
600 College Road East
Suite 2100
Princeton, NJ 08540
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

'x' references

(PCT Rule 44.1)

Date of mailing (day/month/year)	24. 06. 2005
Applicant's or agent's file reference RLL-416WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/IB2004/002648	International filing date (day/month/year) 13/08/2004
Applicant RANBAXY LABORATORIES LIMITED	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders


Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Dominique Hundt
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference RLL-416WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IB2004/002648	International filing date (day/month/year) 13/08/2004	(Earliest) Priority Date (day/month/year) 14/08/2003
Applicant RANBAXY LABORATORIES LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☒ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002648

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/00 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 839 350 A (ATSUMI KUNIO ET AL) 13 June 1989 (1989-06-13) the whole document	1-31, 34
X A	column 24; example 18 Reference Example 1	16-21 32, 33
X	EP 0 658 558 A (BIOCHEMIE GMBH) 21 June 1995 (1995-06-21) the whole document	1-15, 22-31, 34, 37, 38
P, A	WO 03/091230 A (DESHPANDE PANDURANG BALWANT ; KAMMA RAMAKRISHNA (IN); LUTHRA PARVEN KU) 6 November 2003 (2003-11-06) the whole document	1-15, 22-34
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

15 June 2005

Date of mailing of the international search report

24.06.2005

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Deutsch, W

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002648

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 016 665 A (MEIJI SEIKA KAISHA) 5 July 2000 (2000-07-05) the whole document	1-15, 22-31, 34
X	page 4, reaction scheme and paragraph '0008!	32, 33
X	----- US 4 918 068 A (YAMAMOTO ET AL) 17 April 1990 (1990-04-17) example 4	16-21
A	----- EP 0 597 429 A (BIOCHEMIE GESELLSCHAFT M.B.H) 18 May 1994 (1994-05-18) the whole document	32, 33
X	----- SAKAGAMI K ET AL: "SYNTHESIS AND ORAL ACTIVITY OF PIVALOYL OXYMETHYL 7- α -(Z)-2-(2-AMINO THIA ZOL-4-YL)-2-METHOXYIMINOACETAMIDO-3-(Z)-(4-METHYLTHIAZOL-5-YL)VINYL- 3-CEPHEM-4-CARBOXYLATE (ME1207) AND ITS RELATED COMPOUND" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 39, no. 9, September 1991 (1991-09), pages 2433-2436, XP009042230 ISSN: 0009-2363 the whole document	32, 33, 35, 36
A	----- EP 0 723 965 A (MEIJI SEIKA KAISHA LTD; MEIJI SEIKA KAISHA, LTD) 31 July 1996 (1996-07-31) the whole document	32, 33
X	page 7, line 35, ME1206 (sodium salt)	16-23
X	----- US 2002/002279 A1 (YASUI KIYOSHI ET AL) 3 January 2002 (2002-01-03) the whole document	35, 36
X	----- KENJI SAKAGAMI ET AL.: "Synthesis and Oral Activity of ME1207, a New Orally Active Cephalosporin" THE JOURNAL OF ANTIBIOTICS, vol. XLIII, no. 8, 1990, pages 1047-1050, XP009049100 the whole document	32, 33, 35, 36
X	----- US 5 233 035 A (HARA ET AL) 3 August 1993 (1993-08-03) example 38	32, 33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/002648

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15,22-31,34

Claims 1-15:

Subject matter relating to the preparation of cefditoren,
pharmaceutically acceptable salts or ester thereof

2. claims: 16-21

Subject matter relating to a crystalline hydrates of
ceftidoren sodium and crystalline hydrate of ceftidoren
potassium

3. claims: 32-33

Process for the preparation of 7-ATCA (formula IX)

4. claims: Claims 35-38

Subject matter relating to Z-isomers of cefditoren pivoxil
and the Z isomer of 7-ATCA

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. lional Application No

PCT/IB2004/002648

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4839350	A	13-06-1989	JP 62019593 A 28-01-1987
			JP 1698887 C 28-09-1992
			JP 3064503 B 07-10-1991
			JP 61178991 A 11-08-1986
			AT 56017 T 15-09-1990
			CA 1272714 A1 14-08-1990
			CN 85106733 A ,C 14-01-1987
			DE 3579399 D1 04-10-1990
			EP 0175610 A2 26-03-1986
			ES 8704955 A1 01-07-1987
			IE 58487 B1 22-09-1993
			KR 8901196 B1 27-04-1989
EP 0658558	A	21-06-1995	AT 400844 B 25-03-1996
			AT 400843 B 25-03-1996
			AT 233093 A 15-08-1995
			AT 198892 T 15-02-2001
			CN 1107850 A ,C 06-09-1995
			CN 1248581 A 29-03-2000
			DE 69427312 D1 28-06-2001
			DE 69427312 T2 23-08-2001
			DK 658558 T3 17-04-2001
			EP 0658558 A1 21-06-1995
			ES 2155839 T3 01-06-2001
			GR 3035535 T3 29-06-2001
			JP 7188250 A 25-07-1995
			PT 658558 T 29-06-2001
			SI 658558 T1 31-08-2001
			US 5616703 A 01-04-1997
			US 2001016581 A1 23-08-2001
			US 6235897 B1 22-05-2001
			AT 232993 A 15-08-1995
WO 03091230	A	06-11-2003	WO 03091230 A1 06-11-2003
EP 1016665	A	05-07-2000	AT 221890 T 15-08-2002
			AU 731265 B2 29-03-2001
			AU 7933198 A 04-01-1999
			BR 9810313 A 19-09-2000
			CA 2294178 A1 30-12-1998
			DE 69807093 D1 12-09-2002
			DE 69807093 T2 27-03-2003
			EA 2449 B1 25-04-2002
			EP 1016665 A1 05-07-2000
			IL 133681 A 31-10-2003
			NZ 502234 A 29-06-2001
			PL 339361 A1 18-12-2000
			SK 185799 A3 11-07-2000
			US 6288223 B1 11-09-2001
			CN 1107679 C 07-05-2003
			ES 2182330 T3 01-03-2003
			HU 0002458 A2 28-02-2001
			ID 24210 A 13-07-2000
			WO 9858932 A1 30-12-1998
			PT 1016665 T 31-12-2002
			TR 200000310 T2 21-08-2000
US 4918068	A	17-04-1990	JP 62205088 A 09-09-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No
PCT/IB2004/002648

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4918068	A	DE 3789720 D1 DE 3789720 T2 EP 0236231 A2	09-06-1994 18-08-1994 09-09-1987
EP 0597429	A 18-05-1994	AT 400436 B AT 221292 A AT 233267 T DE 69332707 D1 DE 69332707 T2 EP 0597429 A2 ES 2193140 T3 JP 2662176 B2 JP 6247973 A SG 64379 A1 US 2001007029 A1 US 6248881 B1	27-12-1995 15-05-1995 15-03-2003 03-04-2003 16-10-2003 18-05-1994 01-11-2003 08-10-1997 06-09-1994 27-04-1999 05-07-2001 19-06-2001
EP 0723965	A 31-07-1996	DE 69427365 D1 DE 69427365 T2 EP 0723965 A1 US 5827845 A ES 2157989 T3 WO 9509171 A1	05-07-2001 28-02-2002 31-07-1996 27-10-1998 01-09-2001 06-04-1995
US 2002002279	A1 03-01-2002	AT 238310 T AU 714735 B2 AU 4222297 A BR 9712072 A CA 2265686 A1 CN 1234036 A ,C CZ 9900975 A3 DE 69721290 D1 DE 69721290 T2 EA 1526 B1 EP 0937083 A1 ES 2198593 T3 HK 1022912 A1 HU 9903454 A2 ID 22064 A IL 129016 A WO 9812200 A1 JP 3403206 B2 JP 2001500521 T KR 2000048496 A NZ 334883 A PL 332314 A1 PT 937083 T SK 35499 A3 TR 9900614 T2 US 6294669 B1	15-05-2003 13-01-2000 14-04-1998 24-08-1999 26-03-1998 03-11-1999 11-08-1999 28-05-2003 22-01-2004 23-04-2001 25-08-1999 01-02-2004 12-12-2003 28-03-2000 26-08-1999 12-01-2003 26-03-1998 06-05-2003 16-01-2001 25-07-2000 29-09-2000 30-08-1999 29-08-2003 13-03-2000 21-06-1999 25-09-2001
US 5233035	A 03-08-1993	AU 6314890 A CA 2026204 A1 EP 0420608 A2 IE 903455 A1 NZ 235391 A PT 95403 A CN 1050717 A	11-04-1991 27-03-1991 03-04-1991 10-04-1991 25-06-1992 22-05-1991 17-04-1991

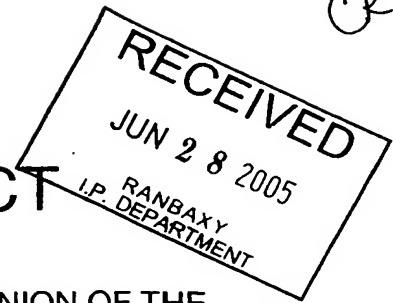
Information on patent family members

PCT/IB2004/002648

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5233035	A	JP 3264590 A	25-11-1991
		DD 298104 A5	06-02-1992

INTERNATIONAL COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2004/002648

International filing date (day/month/year)
13.08.2004

Priority date (day/month/year)
14.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07D501/00, A61K31/545

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Deutsch, W

Telephone No. +49 89 2399-8281



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/IB2004/002648**IAP20 Rec'd PCT/PTO 13 FEB 2006****Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002648

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

☒ paid additional fees.

☐ paid additional fees under protest.

☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

☒ all parts.

☐ the parts relating to claims Nos.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002648

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-34
	No: Claims	35-38
Inventive step (IS)	Yes: Claims	
	No: Claims	1-38
Industrial applicability (IA)	Yes: Claims	1-38
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/002648

IV

This Authority considers that there are 4 inventions covered by the claims indicated as follows:

- 1: Claims 1-15 directed to the preparation of ceftidoren, pharmaceutically acceptable salts or esters thereof
- 2: Claims 16-21, 22-31 directed to crystalline hydrates of ceftidoren sodium and crystalline hydrates of ceftidoren potassium
- 3: Claims 32-33 directed to a process for the preparation of 7-ATCA (formula IX)
- 4: Claims 36-37, 38 directed to Z-isomers of cefidoren pivoxil and the Z isomer of 7-ATCA

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

According to Rule 13.1 PC, an international application shall relate to one invention or to a group of inventions so linked as to form a single inventive concept.

Both ceftidoren and 7-ATCA (see formula IX) are known from the prior art - see the compound of formula a in EP 1016665 a and the compound of formula IA in the document EP 0 658 558 A1.

In view of the above two separate problems can be identified in the claims, namely the problem of providing a further process for the preparation of the known cefditoren and the distinct problem of preparing the known 7-ATCA compound (cf inventions 1 and 3).

EP-a-0 723 965 discloses the sodium salt of cefditoren (see novelty, invention 2). In this case further distinct problems are associated with claims 16-21, namely the provision of further salt forms of cefditoren. The problem and its solution, namely the hydrated forms of claims 16-21 are distinct from those associated with inventions 1 and 3, leading to further unity objections.

Claims 36 and 37 define the claim partially in terms of a process of preparation. It is to be noted that a product is not rendered novel through the fact that it is produced by means of a new process. Thus a claim defining a product in terms of a process is to be construed as a claim to the product as such.

Furthermore, as a rule conventional methods for the purification of low molecular compounds are within the general knowledge of the skilled person, a document disclosing a low molecular weight compound normally makes this compound available to the public in all grades of purity. Thus, the disclosures of EP-A-0 658 558 A1 and EP106665 A1 (page 5, 1st full para and page 2, 3rd para) anticipate claim 35-38. This leads to an a posteriori lack of unity between this claim and the other groups of inventions, since there is no unifying technical contribution over the prior art.

No special technical feature could be identified which defines a contribution over the prior art establishing a technical relationship as required by Rule 13.2 PCT between the above groups of inventions

V

Reference is made to the following documents:

- D1: US-A-4 839 350 (ATSUMI KUNIO ET AL) 13 June 1989 (1989-06-13)
- D2: EP-A-0 658 558 (BIOCHEMIE GMBH) 21 June 1995 (1995-06-21)
- D3: WO 03/091230 A (DESHPANDE PANDURANG BALWANT ; KAMMA RAMAKRISHNA (IN); LUTHRA PARVEN KU) 6 November 2003 (2003-11-06)
- D4: EP-A-1 016 665 (MEIJI SEIKA KAISHA) 5 July 2000 (2000-07-05)
- D5: US-A-4 918 068 (YAMAMOTO ET AL) 17 April 1990 (1990-04-17)
- D6: EP-A-0 597 429 18 May 1994 (1994-05-18)
- D7: SAKAGAMI K ET AL: "SYNTHESIS AND ORAL ACTIVITY OF PIVALOYLOCY METHYL7- \tilde{A} (Z)-2-(2-AMINOTHIA ZOL-4-YL)-2-

METHOXYIMINOACETAMIDOÜ-3-(Z)-(4-METHYLTHIAZOL-5-YL)VINYL- 3-
CEPHEM-4-CARBOXYLATE (ME1207) AND ITS RELATED COMPOUND"
CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL
SOCIETY OF JAPAN, TOKYO, JP, vol. 39, no. 9, September 1991 (1991-09),
pages 2433-2436, XP009042230 ISSN: 0009-2363

D8: EP-A-0 723 965 (MEIJI SEIKA KAISHA LTD; MEIJI SEIKA KAISHA, LTD) 31
July 1996 (1996-07-31)

D9: US 2002/002279 A1 (YASUI KIYOSHI ET AL) 3 January 2002 (2002-01-03)

D10: SAKAGAMI ET AL; THE JOURNAL OF ANTIBIOTICS, vol. XLIII, no.8, 1047-

D11: US5233035 A(HARA ET AL) 3 August 1993 (1993-08-03)

Invention 1

Novelty

The process of the present claims 1,22,31,34 is considered to be a novel selection from D1 (cf column 7, line 14- column 12, line 66).

The compound of formula Ia according to D2 corresponds to the compound of IX (7-ATCA) as given in the present claim 1. D2 further discloses that this intermediate is a central intermediate in the production of cefditoren pivoxil. D2 however does not disclose directly the process by which 7-ATCA is converted into cefditoren, such that the present claims 1,22,31,34 is novel vis-a-vis D2.

The present claims 1, 22, 31, 34 differ from D4 through the reaction of the compounds of formula IX with the compounds of formula X (cf e.g. claim 7 of D4).

Inventive Step

The closest prior art is considered to be D1, since the present process of claim 1 is a selection from the process of D1 (see column 7, line 14-column 12, line 66).

In particular compound III of D1 may be in the form of a reactive acid derivative, wherein such a derivative is made reactive at the carboxyl group. Examples of the reactive derivative at the carboxyl group include a diphenylphosphoric acid, dialkylphosphoric. (cf column 8 of D1).

In view of the above the skilled person could have arrived at the claimed subject matter (qualitatively) by considering the general disclosure of reactive derivatives of formula III and further alternatives to those specifically disclosed.

The problem underlying the present invention is thus considered to be the provision of a process having surprising effects compared to the prior art.

According to the description the claimed process provides a process wherein the desired Z-isomer of cefditoren and salts and esters thereof are obtained without involving the purification of either the intermediates or the final product for removing the E-isomer. This is not reflected in the claims, which appear to be generally directed to the formation of cefditoren, salts and esters thereof from the compound of formula X, without regard to the isomeric forms of the products or reactants, such that at present an inventive step cannot be acknowledged.

Invention 2

Novelty

The present claims 16 and 17 differ the starting material in example 4 of D5 and the sodium salt of cefditoren disclosed in D8 (see the ME1206 (sodium salt; page 7, line 35 of 10) through the hydration of the sodium salt of cefditoren.

Inventive Step

The closest prior art is considered to be D8 as this discloses the sodium salt of cefditoren and its use as an antibiotic.

The use of a sodium salt of cefditoren is known from D8, such that the skilled person would have at least qualitatively have considered the claimed subject matter of invention 2.

Furthermore the skilled person would consider salt formation as a means of increasing solubility compared to the free compound.

The problem underlying invention 2, is considered to be the provision of further salt forms of cefditoren, which have surprising effects compared to the closest prior art. In the absence of such effects an inventive step cannot be acknowledged

Invention 3

Novelty

The process of the present claims 32 and 33 differs from that of D1, D6 and D8 inter alia through the phenacetyl amino protecting group.

The process of the present claims 32 and differs from that of D7, D10 and D11 through the removal of the R protecting group from the compound of formula VII.

Inventive Step

The closest prior art is considered to be D7, D10 or D11.

The only difference between the process of "invention 3" and that of D7, D10 or D11 is that the carboxyl protecting group is removed so as to form 7-ATCA, otherwise all other steps are the same.

It is considered that the skilled person wishing to form 7-ATCA would consider removing the carboxyl protecting group in the D7, D10 and D11 processes, such that the process of "invention 3" is obvious at least qualitatively.

The problem underlying invention 3 is considered to be the provision of a novel process for

the preparation of 7-ATCA, having a surprising effect compared to the prior art. IN the absence of any evidence for such an effect an inventive step cannot be acknowledged.

Invention 4

Novelty

As indicated in the section on unity the disclosures EP-a-0 658558 (D2) anticipate the disclosures of claims 35-38 (see inter alia page 4, lines 5-40).

Similarly EP106665 A1 (D4) (page 5, 1st full para and page 2, 3rd para) is novelty destroying for claim 37 (cf also section on non unity).

Me1206 disclosed in D7 and D10 are novelty destroying to claims 35 and 36.

Inventive Step

In view of the disclosures of D4, D7 and D10 it is unclear at present where the inventiveness of "invention 4" could lie.

VI

For the purposes of this communication it has been assumed that the priority of the present application is valid.

D3 does not constitute prior art within the meaning of Rule 64.1 (b).

VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D11 is not mentioned in the description, nor are these documents identified therein.